Product-form stationary distributions for deficiency zero chemical reaction networks

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Abstract

We consider stochastically modeled chemical reaction systems with mass-action kinetics and prove that a product-form stationary distribution exists for each closed, irreducible subset of the state space if an analogous deterministically modeled system with mass-action kinetics admits a complex balanced equilibrium. Feinberg's deficiency zero theorem then implies that such a distribution exists so long as the corresponding chemical network is weakly reversible and has a deficiency of zero. The main parameter of the stationary distribution for the stochastically modeled system is a complex balanced equilibrium value for the corresponding deterministically modeled system. We also generalize our main result to some non-mass-action kinetics.

1 Introduction

There are two commonly used models for chemical reaction systems: discrete stochastic models in which the state of the system is a vector giving the number of each molecular species, and continuous deterministic models in which the state of the system is a vector giving the concentration of each molecular species. Discrete stochastic models are typically used when the number of molecules of each chemical species is low and the randomness inherent in the making and breaking of chemical bonds is important. Conversely, deterministic models are used when there are large numbers of molecules for each species and the behavior of the concentration of each species is well approximated by a coupled set of ordinary differential equations.

Typically, the goal in the study of discrete stochastic systems is to either understand the evolution of the distribution of the state of the system or to find the long term stationary distribution of the system, which is the stochastic analog of an equilibrium point. The Kolmogorov forward equation (chemical master equation in the chemistry literature) describes the evolution of the distribution and so work has been done in trying to analyze or solve the forward equation for certain classes of systems ([20]). However, it is typically an extremely difficult task to solve or even numerically compute the solution to the forward equation for all but the simplest of systems. Therefore, simulation methods have been developed that will generate sample paths so as to approximate the distribution of the state via Monte Carlo methods. These simulation methods include algorithms

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that generate statistically exact ([1, 22, 23, 21]) and approximate ([3, 5, 24, 9]) sample paths. On the other hand, the continuous deterministic models, and in particular mass-action systems with complex balancing states, have been analyzed extensively in the mathematical chemistry literature, starting with the works of Horn, Jackson, and Feinberg ([26, 27, 28, 15]), and continuing with Feinberg's deficiency theory in ([16, 17, 18, 19]). Such models have a wide range of applications in the physical sciences, and now they are beginning to play an important role in systems biology ([13, 25, 37]). Recent mathematical analysis of continuous deterministic models has focused on their potential to admit multiple equilibria ([11, 12]) and on dynamical properties such as persistence and global stability ([37, 7, 2, 4, 6]).

One of the major theorems pertaining to deterministic models of chemical systems is the deficiency zero theorem of Feinberg ([17, 16]). The deficiency zero theorem states that if the network of a system satisfies certain easily checked properties, then within each compatibility class (invariant manifold in which a solution is confined) there is precisely one equilibrium with strictly positive components, and that equilibrium is locally asymptotically stable ([17, 16]). The surprising aspect of the deficiency zero theorem is that the assumptions of the theorem are completely related to the network of the system whereas the conclusions of the theorem are related to the dynamical properties of the system. We will show in this paper that if the conditions of the deficiency zero theorem hold on the network of a stochastically modeled chemical system with quite general kinetics, then there exists a product-form stationary distribution for each closed, irreducible subset of the state space. In fact, we will show a stronger result: that a product-form stationary distribution exists so long as there exists a complex balanced equilibrium for the associated deterministically modeled system. However, the equilibrium values guaranteed to exist by the deficiency zero theorem are complex balanced and so the conditions of that theorem are sufficient to guarantee the existence of the product-form distribution. Finally, the main parameter of the stationary distribution will be shown to be a complex balanced equilibrium value of the deterministically modeled system.

Product-form stationary distributions play a central role in the theory of queueing networks where the product-form property holds for a large, naturally occurring class of models called Jackson networks (see, for example, [30], Chapter 3, and [10], Chapter 2) and a much larger class of quasi-reversible networks ([30], Chapter 3, [10], Chapter 4, [36], Chapter 8). Kelly, [30], Section 8.5, recognizes the possible existence of product-form stationary distributions for a subclass of chemical reaction models and gives a condition for that existence. That condition is essentially the complex balance condition described below, and our main result asserts that for any mass-action chemical reaction model the conditions of the deficiency zero theorem ensure that this condition holds.

The outline of the paper is as follows. In Section 2 we formally introduce chemical reaction networks. In Section 3 we develop both the stochastic and deterministic models of chemical reaction systems. Also in Section 3 we state the deficiency zero theorem for deterministic systems and present two theorems that are used in its proof and that will be of use to us. In Section 4 we present the first of our main results: that every closed, irreducible subset of the state space of a stochastically modeled system with mass-action kinetics has a product-form stationary distribution if the chemical network is weakly reversible and has a deficiency of zero. In Section 5 we present some examples of the use of this result. In Section 6 we extend our main result to systems with more general kinetics.

2 Chemical reaction networks

Consider a system with m chemical species, $\{S_1, \ldots, S_m\}$, undergoing a finite series of chemical reactions. For the kth reaction, denote by $\nu_k, \nu_k' \in \mathbb{Z}^m_{\geq 0}$ the vectors representing the number of molecules of each species consumed and created in one instance of that reaction, respectively. We note that if $\nu_k = \vec{0}$ then the kth reaction represents an input to the system, and if $\nu_k' = \vec{0}$ then it represents an output. Using a slight abuse of notation, we associate each such ν_k (and ν_k') with a linear combination of the species in which the coefficient of S_i is ν_{ik}, the ith element of ν_k. For example, if $\nu_k = [1,\ 2,\ 3]^T$ for a system consisting of three species, we associate with ν_k the linear combination $S_1 + 2S_2 + 3S_3$. For $\nu_k = \vec{0}$, we simply associate ν_k with $\emptyset$. Under this association, each ν_k (and ν_k') is termed a *complex* of the system. We denote any reaction by the notation $\nu_k \to \nu_k'$, where ν_k is the source, or reactant, complex and ν_k' is the product complex. We note that each complex may appear as both a source complex and a product complex in the system. The set of all complexes will be denoted by $\{\nu_k\} := \cup_k(\{\nu_k\} \cup \{\nu_k'\})$.

Definition 2.1. Let $\mathcal{S} = \{S_i\}$, $\mathcal{C} = \{\nu_k\}$, and $\mathcal{R} = \{\nu_k \to \nu_k'\}$ denote the sets of species, complexes, and reactions, respectively. The triple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is called a *chemical reaction network*.

The structure of chemical reaction networks plays a central role in both the study of stochastically and deterministically modeled systems. As alluded to in the Introduction, it will be conditions on the network of a system that guarantee certain dynamical properties for both models. Therefore, the remainder of this section consists of definitions related to chemical networks that will be used throughout the paper.

Definition 2.2. A chemical reaction network, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, is called *weakly reversible* if for any reaction $\nu_k \to \nu_k'$, there is a sequence of directed reactions beginning with ν_k' as a source complex and ending with ν_k as a product complex. That is, there exist complexes $\nu_1, \ldots, \nu_r$ such that $\nu_k' \to \nu_1, \nu_1 \to \nu_2, \ldots, \nu_r \to \nu_k \in \mathcal{R}$. A network is called *reversible* if $\nu_k' \to \nu_k \in \mathcal{R}$ whenever $\nu_k \to \nu_k' \in \mathcal{R}$.

Remark. The definition of a reversible network given in Definition 2.2 is distinct from the notion of a reversible stochastic process. However, in Section 4.2 we point out a connection between the two concepts for systems that are detailed balanced.

To each reaction network, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, there is a unique, directed graph constructed in the following manner. The nodes of the graph are the complexes, $\mathcal{C}$. A directed edge is then placed from complex ν_k to complex ν_k' if and only if $\nu_k \to \nu_k' \in \mathcal{R}$. Each connected component of the resulting graph is termed a *linkage class* of the graph. We denote the number of linkage classes by ℓ. It is easy to see that a chemical reaction network is weakly reversible if and only if each of the linkage classes of its graph is strongly connected.

Definition 2.3. $S = \text{span}_{\{\nu_k \to \nu_k' \in \mathcal{R}\}}\{\nu_k' - \nu_k\}$ is the *stoichiometric subspace* of the network. For $c \in \mathbb{R}^m$ we say $c + S$ and $(c + S) \cap \mathbb{R}^m_{>0}$ are the *stoichiometric compatibility classes* and *positive stoichiometric compatibility classes* of the network, respectively. Denote $\dim(S) = s$.

It is simple to show that for both stochastic and deterministic models, the state of the system remains within a single stoichiometric compatibility class for all time, assuming that one starts

in that class. This fact is important because it changes the types of questions that are reasonable to ask about a given system. For example, unless there is only one stoichiometric compatibility class, and so $S = \mathbb{R}^m$, the correct question is not whether there is a unique fixed point for a given deterministic system. Instead, the correct question is *whether within each stoichiometric compatibility class* there is a unique fixed point. Analogously, for stochastically modeled systems it is typically of interest to compute stationary distributions for each closed, irreducible subset of the state space (each contained within a stoichiometric compatibility class) with the precise subset being determined by initial conditions.

The final definition of this section is that of the *deficiency* of a network ([16]). It is not a difficult exercise to show that the deficiency of a network is always greater than or equal to zero.

Definition 2.4. The *deficiency* of a chemical reaction network, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, is $\delta = |\mathcal{C}| - \ell - s$, where $|\mathcal{C}|$ is the number of complexes, ℓ is the number of linkage classes of the network graph, and s is the dimension of the stoichiometric subspace of the network.

While the deficiency is, by definition, only a property of the network, we will see in Sections 3.2, 4, and 6 that a deficiency of zero has implications for the long-time dynamics of both deterministic and stochastic models of chemical reaction systems.

3 Dynamical models

The notion of a chemical reaction network is the same for both stochastic and deterministic systems and the choice of whether to model the evolution of the state of the system stochastically or deterministically is made based upon the details of the specific chemical or biological problem at hand. Typically if the number of molecules is low, a stochastic model is used, and if the number of molecules is high, a deterministic model is used. For cases between the two extremes a diffusion approximation can be used or, for cases in which the system contains multiple scales, pieces of the reaction network can be modeled stochastically, while others can be modeled deterministically (or, more accurately, absolutely continuously with respect to time). See, for example, [8] and Section 5.1.

3.1 Stochastic models

The simplest stochastic model for a chemical network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ treats the system as a continuous time Markov chain whose state $X \in \mathbb{Z}^m_{\geq 0}$ is a vector giving the number of molecules of each species present with each reaction modeled as a possible transition for the state. We assume a finite number of reactions. The model for the kth reaction, $\nu_k \to \nu'_k$, is determined by the vector of inputs, ν_k, specifying the number of molecules of each chemical species that are consumed in the reaction, the vector of outputs, ν'_k, specifying the number of molecules of each species that are created in the reaction, and a function of the state, $\lambda_k(X)$, that gives the rate at which the reaction occurs. Specifically, if the kth reaction occurs at time t, the new state becomes

$$X(t) = X(t-) + \nu'_k - \nu_k.$$

Let $R_k(t)$ denote the number of times that the kth reaction occurs by time t. Then the state of the system at time t can be written as

$$X(t) = X(0) + \sum_k R_k(t)(\nu_k' - \nu_k), \tag{3.1}$$

where we have summed over the reactions. The process R_k is a counting process with intensity $\lambda_k(X(t))$ (called the *propensity* in the chemistry literature) and can be written as

$$R_k(t) = Y_k\left(\int_0^t \lambda_k(X(s))ds\right), \tag{3.2}$$

where the Y_k are independent, unit-rate Poisson processes ([32], [14] Ch. 11). Note that (3.1) and (3.2) give a system of stochastic equations that uniquely determines X up to $\sup\{t : \sum_k R_k(t) < \infty\}$. The generator for the Markov chain is the operator, A, defined by

$$Af(x) = \sum_k \lambda_k(x)(f(x + \nu_k' - \nu_k) - f(x)), \tag{3.3}$$

where f is any function defined on the state space.

A commonly chosen form for the intensity functions λ_k is that of stochastic mass-action, which says that for $x \in \mathbb{Z}_{\geq 0}^m$ the rate of the kth reaction should be given by

$$\lambda_k(x) = \kappa_k\left(\prod_{\ell=1}^m \nu_{\ell k}!\right)\binom{x}{\nu_k} = \kappa_k \prod_{\ell=1}^m \frac{x_\ell!}{(x_\ell - \nu_{\ell k})!} 1_{\{x_\ell \geq \nu_{\ell k}\}}, \tag{3.4}$$

for some constant κ_k, where we adopt the convention that $0! = 1$. Note that the rate (3.4) is proportional to the number of distinct subsets of the molecules present that can form the inputs for the reaction. Intuitively, this assumption reflects the idea that the system is *well-stirred* in the sense that all molecules are equally likely to be at any location at any time. For concreteness, we will assume that the intensity functions satisfy (3.4) throughout most of the paper. In Section 6 we will generalize our results to systems with more general kinetics.

A probability distribution $\{\pi(x)\}$ is a stationary distribution for the chain if

$$\sum_x \pi(x)Af(x) = 0$$

for a sufficiently large class of functions f or, taking $f(y) = \mathbf{1}_x(y)$ and using equation (3.3), if

$$\sum_k \pi(x - \nu_k' + \nu_k)\lambda_k(x - \nu_k' + \nu_k) = \pi(x)\sum_k \lambda_k(x) \tag{3.5}$$

for all x in the state space. If the network is weakly reversible, then the state space of the Markov chain is a union of closed, irreducible communicating classes. (This fact follows because if the Markov chain can proceed from state x to state y via a sequence of reactions, weak reversibility of the network implies those reactions can be "undone" in reverse sequential order by another

sequence of reactions.) Also, each closed, irreducible communicating class is either finite or countable. Therefore, if a stationary distribution with support on a single communicating class exists it is unique and

$$\lim_{t\to\infty} P(X(t) = x \mid X(0) = y) = \pi(x),$$

for all x, y in that communicating class. Thus, the stationary distribution gives the long-term behavior of the system.

Solving equation (3.5) is in general a formidable task. However, in Section 4 we will do so if the network is weakly reversible, has a deficiency of zero, and if the rate functions $\lambda_k(x)$ satisfy mass-action kinetics, (3.4). We will also show that the stationary distribution is of product form. More specifically, we will show that for each communicating class there exists a $c \in \mathbb{R}^m_{>0}$ and a normalizing constant $M > 0$ such that

$$\pi(x) = M \prod_{i=1}^{m} \pi_i(x_i) := M \prod_{i=1}^{m} \frac{c_i^{x_i}}{x_i!}$$

satisfies equation (3.5). The c_i in the definition of π_i will be shown to be the ith component of an equilibrium value of the analogous deterministic system described in the next section. In Section 6 we will solve (3.5) for more general kinetics.

3.2 Deterministic models and the deficiency zero theorem

Under an appropriate scaling limit (see Section 4.1) the continuous time Markov chain (3.1), (3.2), (3.4) becomes

$$x(t) = x(0) + \sum_k \left(\int_0^t f_k(x(s))ds \right) (\nu'_k - \nu_k) := x(0) + \int_0^t f(x(s))ds, \tag{3.6}$$

where the last equality is a definition and

$$f_k(x) = \kappa_k x_1^{\nu_{1k}} x_2^{\nu_{2k}} \cdots x_m^{\nu_{mk}}, \tag{3.7}$$

where we use the convention $0^0 = 1$. We say that the deterministic system (3.6) has *mass-action kinetics* if the rate functions f_k have the form (3.7). The proof of the following theorem by Feinberg can be found in [16] or [19]. We note that the full statement of the deficiency zero theorem actually says more than what is given below and the interested reader is encouraged to see the original work.

Theorem 3.1 (The Deficiency Zero Theorem)**.** *Consider a weakly reversible, deficiency zero chemical reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ with dynamics given by* (3.6)-(3.7)*. Then for any choice of rate constants $\{\kappa_k\}$, within each positive stoichiometric compatibility class there is precisely one equilibrium value, and that equilibrium value is locally asymptotically stable relative to its compatibility class.*

The dynamics of the system (3.6)-(3.7) take place in $\mathbb{R}^m_{\geq 0}$. However, to prove the deficiency zero theorem it turns out to be more appropriate to work in *complex space*, denoted $\mathbb{R}^{\mathcal{C}}$, which we will describe now. For any $U \subseteq \mathcal{C}$ let $\omega_U : \mathcal{C} \to \{0, 1\}$ denote the indicator function $\omega_U(\nu_k) =$

$\mathbf{1}_{\{\nu_k \in U\}}$. Complex space is defined to be the vector space with basis $\{\omega_{\nu_k} \mid \nu_k \in \mathcal{C}\}$, where we have denoted $\omega_{\{\nu_k\}}$ by ω_{ν_k}.

If u is a vector with nonnegative integer components and w is a vector with nonnegative real components, then let $u! = \prod_i u_i!$ and $w^u = \prod_i w_i^{u_i}$, where we interpret $0^0 = 1$ and $0! = 1$. Let $\Psi : \mathbb{R}^m \to \mathbb{R}^{\mathcal{C}}$ and $A_\kappa : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ be defined by:

$$\Psi(x) = \sum_{\nu_k \in \mathcal{C}} x^{\nu_k} \omega_{\nu_k}$$
$$A_\kappa(y) = \sum_{\nu_k \to \nu_k' \in \mathcal{R}} \kappa_k y_{\nu_k} (\omega_{\nu_k'} - \omega_{\nu_k}),$$

where the subscript κ of A_κ denotes the choice of rate constants for the system. Let $Y : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^m$ be the linear map whose action on the basis elements $\{\omega_{\nu_k}\}$ is defined by $Y(\omega_{\nu_k}) = \nu_k$. Then equations (3.6)-(3.7) can be written as the coupled set of ordinary differential equations

$$\dot{x}(t) = f(x(t)) = Y(A_\kappa(\Psi(x(t)))).$$

Therefore, in order to show that a value c is an equilibrium of the system, it is sufficient to show that $A_\kappa(\Psi(c)) = 0$, which is an explicit system of equations for c. In particular, $A_k(\Psi(c)) = 0$ if and only if for each $z \in \mathcal{C}$

$$\sum_{\{k:\nu_k' = z\}} \kappa_k c^{\nu_k} = \sum_{\{k:\nu_k = z\}} \kappa_k c^{\nu_k}, \tag{3.8}$$

where the sum on the left is over reactions for which z is the product complex and the sum on the right is over reactions for which z is the source complex.

The following has been shown in [28] and [16] (see also [25]).

Theorem 3.2. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network with dynamics given by* (3.6)-(3.7) *for some choice of rate constants, $\{\kappa_k\}$. Suppose there exists a $c \in \mathbb{R}^m_{>0}$ for which $A_\kappa(\Psi(c)) = 0$, then the following hold:*

1. *The network is weakly reversible.*
2. *Every equilibrium point with strictly positive components, $x \in \mathbb{R}^m_{>0}$ with $f(x) = 0$, satisfies $A_\kappa(\Psi(x)) = 0$.*
3. *If $Z = \{x \in \mathbb{R}^m_{>0} \mid f(x) = 0\}$, then $\ln Z := \{y \in \mathbb{R}^m \mid \exists\ x \in Z$ and $y_i = \ln(x_i)\}$ is a coset of $S^\perp$, the perpendicular complement of S. That is, there is a $k \in \mathbb{R}^m$ such that $\ln Z = \{w \in \mathbb{R}^m \mid w = k + u$ for some $u \in S^\perp\}$.*
4. *There is one, and only one, equilibrium point in each positive stoichiometric compatibility class.*
5. *Each equilibrium point of a positive stoichiometric compatibility class is locally asymptotically stable relative to its stoichiometric compatibility class.*

Thus, after a choice of rate constants has been made, the conclusions of the deficiency zero theorem pertaining to the existence and asymptotic stability of equilibria (points $4.$ and $5.$ of Theorem 3.2) hold so long as there exists at least one $c \in \mathbb{R}^m_{>0}$ such that $A_\kappa(\Psi(c)) = 0$. The condition that the system has a deficiency of zero only plays a role in showing that there does exist such a $c \in \mathbb{R}^m_{>0}$. A proof of the following can be found in [16], [17], or [19].

Theorem 3.3. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network with dynamics given by* (3.6)-(3.7) *for some choice of rate constants, $\{\kappa_k\}$. If the network has a deficiency of zero, then there exists a $c \in \mathbb{R}^m_{>0}$ such that $A_\kappa(\Psi(c)) = 0$ if and only if the network is weakly reversible.*

A chemical reaction network with deterministic mass-action kinetics (and a choice of rate constants) that admits a c for which $A_\kappa(\Psi(c)) = 0$ is called *complex balanced* in the literature. The second conclusion of Theorem 3.2 demonstrates why this notation is appropriate. The equivalent representation given by (3.8) shows the origin of this terminology. The surprising aspect of the deficiency zero theorem is that it gives simple and checkable sufficient conditions on the network structure alone that guarantee that a system is complex balanced for any choice of rate constants. We will see in the following sections that the main results of this paper have the same property: product-form stationary distributions exist for all stochastic systems that are complex balanced when viewed as deterministic systems, and $\delta = 0$ is a sufficient condition to guarantee this for weakly reversible networks.

4 Main result for mass-action systems

The collection of stationary distributions for a countable state space Markov chain is convex. The extremal distributions correspond to the closed, irreducible subsets of the state space; that is, every stationary distribution can be written as

$$\pi = \sum_{\Gamma} \alpha_\Gamma \pi_\Gamma, \tag{4.1}$$

where $\alpha_\Gamma \geq 0$, $\sum_\Gamma \alpha_\Gamma = 1$, and the sums are over the closed, irreducible subsets Γ of the state space. Here π_Γ is the unique stationary distribution satisfying $\pi_\Gamma(\Gamma) = 1$.

We now state and prove our main result for systems with mass-action kinetics.

Theorem 4.1. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network and let $\{\kappa_k\}$ be a choice of rate constants. Suppose that, modeled deterministically, the system is complex balanced with complex balanced equilibrium $c \in \mathbb{R}^m_{>0}$. Then the stochastically modeled system with intensities* (3.4) *has a stationary distribution consisting of the product of Poisson distributions,*

$$\pi(x) = \prod_{i=1}^m \frac{c_i^{x_i}}{x_i!} e^{-c_i}, \qquad x \in \mathbb{Z}^m_{\geq 0}. \tag{4.2}$$

If $\mathbb{Z}^m_{\geq 0}$ is irreducible, then (4.2) *is the unique stationary distribution, whereas if $\mathbb{Z}^m_{\geq 0}$ is not irreducible then the π_Γ of equation* (4.1) *are given by the product-form stationary distributions*

$$\pi_\Gamma(x) = M_\Gamma \prod_{i=1}^m \frac{c_i^{x_i}}{x_i!}, \qquad x \in \Gamma,$$

and $\pi_\Gamma(x) = 0$ otherwise, where M_Γ is a positive normalizing constant.

Proof. Let π satisfy (4.2) where $c \in \mathbb{R}^m_{>0}$ satisfies $A_\kappa(\Psi(c)) = 0$. We will show that π is stationary by verifying that equation (3.5) holds for all $x \in \mathbb{Z}^m_{\geq 0}$. Plugging π and (3.4) into equation (3.5) and simplifying yields

$$\sum_k \kappa_k c^{\nu_k - \nu'_k} \frac{1}{(x-\nu'_k)!} \prod_{\ell=1}^m 1_{\{x_\ell \geq \nu'_{\ell k}\}} = \sum_k \kappa_k \frac{1}{(x-\nu_k)!} \prod_{\ell=1}^m 1_{\{x_\ell \geq \nu_{\ell k}\}}. \tag{4.3}$$

Equation (4.3) will be satisfied if for each complex $z \in \mathcal{C}$,

$$\sum_{\{k:\nu'_k = z\}} \kappa_k c^{\nu_k - z} \frac{1}{(x-z)!} \prod_{\ell=1}^m 1_{\{x_\ell \geq z_\ell\}} = \sum_{\{k:\nu_k = z\}} \kappa_k \frac{1}{(x-z)!} \prod_{\ell=1}^m 1_{\{x_\ell \geq z_\ell\}}, \tag{4.4}$$

where the sum on the left is over reactions for which z is the product complex and the sum on the right is over reactions for which z is the source complex. The complex z is fixed in the above equation, and so (4.4) is equivalent to (3.8), which is equivalent to $A_\kappa(\Psi(c)) = 0$.

To complete the proof, one need only observe that the normalized restriction of π to any closed, irreducible subset Γ must also be a stationary distribution. □

The following theorem gives simple and checkable conditions that guarantee the existence of a product-form stationary distribution of the form (4.2).

Theorem 4.2. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network that has a deficiency of zero and is weakly reversible. Then for any choice of rate constants $\{\kappa_k\}$ the stochastically modeled system with intensities* (3.4) *has a stationary distribution consisting of the product of Poisson distributions,*

$$\pi(x) = \prod_{i=1}^m \frac{c_i^{x_i}}{x_i!} e^{-c_i}, \qquad x \in \mathbb{Z}^m_{\geq 0},$$

where c is an equilibrium value for the deterministic system (3.6)-(3.7)*, which is guaranteed to exist and be complex balanced by Theorems 3.1-3.3. If $\mathbb{Z}^m_{\geq 0}$ is irreducible, then π is the unique stationary distribution, whereas if $\mathbb{Z}^m_{\geq 0}$ is not irreducible then the π_Γ of equation* (4.1) *are given by the product-form stationary distributions*

$$\pi_\Gamma(x) = M_\Gamma \prod_{i=1}^m \frac{c_i^{x_i}}{x_i!}, \qquad x \in \Gamma,$$

and $\pi_\Gamma(x) = 0$ otherwise, where M_Γ is a positive normalizing constant.

Proof. This is a direct result of Theorems 3.3 and 4.1. □

We remark that Theorems 4.1 and 4.2 give sufficient conditions under which $\mathbb{Z}^m_{\geq 0}$ being irreducible guarantees that when in distributional equilibrium the species numbers: (a) are independent and (b) have Poisson distributions. We return to this point in Examples 5.2 and 5.3.

4.1 The classical scaling

Defining $|\nu_k| = \sum_i \nu_{ik}$ and letting V be a scaling parameter usually taken to be the volume of the system times Avogadro's number, it is reasonable to scale the rate constants of the stochastic model with the volume like

$$\kappa_k = \frac{\hat{\kappa}_k}{V^{|\nu_k|-1}}, \tag{4.5}$$

for some $\hat{\kappa}_k > 0$. This follows by considering the probability of a particular set of $|\nu_k|$ molecules finding each other in a volume proportional to V in a time interval $[t, t+\Delta t)$. In this case, the intensity functions become

$$\lambda_k^V(x) = \frac{\hat{\kappa}_k}{V^{|\nu_k|-1}}(\prod_i \nu_{ik}!)\binom{x}{\nu_k} = V\hat{\kappa}_k \frac{1}{V^{|\nu_k|}} \prod_i \frac{x_i!}{(x_i-\nu_{ik})!}. \tag{4.6}$$

Since V is the volume times Avogadro's number and x gives the number of molecules of each species present, $c = V^{-1}x$ gives the concentrations in moles per unit volume. With this scaling and a large volume limit

$$\lambda_k^V(x) \approx V\hat{\kappa}_k \prod_i c_i^{\nu_{ik}} = V\hat{\kappa}_k c^{\nu_k} \equiv V\hat{\lambda}_k(c). \tag{4.7}$$

Since the law of large numbers for the Poisson process implies $V^{-1}Y_k(Nu) \approx u$, (3.2) and (4.7), together with the assumption that $X(0) = VC(0)$ for some $C(0) \in \mathbb{R}^m_{>0}$, imply

$$C(t) = V^{-1}X(t) \approx C(0) + \sum_k \int_0^t \hat{\kappa}_k C(s)^{\nu_k} ds\, (\nu_k' - \nu_k),$$

which in the large volume limit gives the classical deterministic law of mass action detailed in Section 3.2. For a precise formulation of the above scaling argument, termed the "classical scaling," see [31, 32, 33].

Because the above scaling is the natural relationship between the stochastic and deterministic models of chemical reaction networks, we expect to be able to generalize Theorem 4.1 to this setting.

Theorem 4.3. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network. Suppose that, modeled deterministically with rate constants $\{\hat{\kappa}_k\}$, the system is complex balanced with complex balanced equilibrium $c \in \mathbb{R}^m_{>0}$. For some $V > 0$, let $\{\kappa_k\}$ be related to $\{\hat{\kappa}_k\}$ via* (4.5)*. Then the stochastically modeled system with intensities* (3.4) *and rate constants $\{\kappa_k\}$ has a stationary distribution consisting of the product of Poisson distributions,*

$$\pi(x) = \prod_{i=1}^m \frac{(Vc_i)^{x_i}}{x_i!} e^{-Vc_i}, \qquad x \in \mathbb{Z}^m_{\geq 0}.$$

If $\mathbb{Z}^m_{\geq 0}$ is irreducible, then (4.2) *is the unique stationary distribution, whereas if $\mathbb{Z}^m_{\geq 0}$ is not irreducible then the π_Γ of equation* (4.1) *are given by the product-form stationary distributions*

$$\pi_\Gamma(x) = M_\Gamma \prod_{i=1}^m \frac{(Vc_i)^{x_i}}{x_i!}, \qquad x \in \Gamma,$$

and $\pi_\Gamma(x) = 0$ otherwise, where M_Γ is a positive normalizing constant.

Proof. The proof is similar to before, and now consists of making sure the V's cancel in an appropriate manner. The details are omitted. □

We see that Theorem 4.1 follows from Theorem 4.3 by taking $V = 1$. Theorem 4.2 generalizes in the obvious way.

4.2 Reversibility and detail balance

An equilibrium value, $c \in \mathbb{R}^m_{>0}$, for a reversible, in the sense of Definition 2.2, chemical reaction network with deterministic mass-action kinetics is called *detailed balanced* if for each pair of reversible reactions, $\nu_k \rightleftarrows \nu'_k$, we have

$$\kappa_k c^{\nu_k} = \kappa'_k c^{\nu'_k}, \tag{4.8}$$

where κ_k, κ'_k are the rate constants for the reactions $\nu_k \to \nu'_k, \nu'_k \to \nu_k$, respectively. In [18], page 1820, Feinberg shows that if one positive equilibrium is detailed balanced then they all are; a result similar to the second conclusion of Theorem 3.2 for complex balanced systems. A reversible chemical reaction system with deterministic mass action kinetics is therefore called *detailed balanced* if it admits one detailed balanced equilibrium. It is immediate that any system that is detailed balanced is also complex balanced. The fact that a product-form stationary distribution of the form (4.2) exists for the stochastic systems whose deterministic analogs are detailed balanced is well-known. See, for example, [38]. Theorems 4.1 and 4.2 can therefore be viewed as an extension of that result. However, more can be said in the case when the deterministic system is detailed balanced, and which we include here for completeness (no originality is being claimed).

As mentioned in the remark following Definition 2.2, the term "reversible" has a meaning in the context of stochastic processes that differs from that of Definition 2.2. Before defining this, we need the concept of a transition rate. For any continuous time Markov chain with state space Γ, the *transition rate* from $x \in \Gamma$ to $y \in \Gamma$ (with $x \neq y$) is a non-negative number $\alpha(x, y)$ satisfying

$$P(X(t + \Delta t) = y \mid X(t) = x) = \alpha(x, y)\Delta t + o(\Delta t).$$

Thus, in the context of this paper, if $y = x + \nu'_k - \nu_k$ for some k, then $\alpha(x, y) = \lambda_k(x)$, and zero otherwise.

Definition 4.4. A continuous time Markov chain $X(t)$ with transition rates $\alpha(x, y)$ is *reversible with respect to the distribution* π if for all x, y in the state space Γ

$$\pi(x)\alpha(x, y) = \pi(y)\alpha(y, x). \tag{4.9}$$

It is simple to see (by summing both sides of (4.9) with respect to y over Γ), that π must be a stationary distribution for the process. A stationary distribution satisfying (4.9) is even called *detailed balanced* in the probability literature. The following is proved in [38], Chapter 7.

Theorem 4.5. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reversible[2] chemical reaction network with rate constants $\{\kappa_k\}$. Then the deterministically modeled system with mass-action kinetics has a detailed balanced equilibrium if and only if the stochastically modeled system with intensities* (3.4) *is reversible with respect to its stationary distribution.*[3]

Succinctly, this theorem says that reversibility and detailed balanced in the deterministic setting is equivalent to reversible (and, hence, detailed balanced) in the stochastic setting.

4.3 Non-uniqueness of c

For stochastically modeled chemical reaction systems any irreducible subset of the state space, Γ, is contained within $(y+S)\cap\mathbb{Z}^m_{\geq 0}$ for some $y\in\mathbb{R}^m_{\geq 0}$. Therefore, each Γ is associated with a stoichiometric compatibility class. For weakly reversible systems with a deficiency of zero, Theorems 3.2 and 3.3 guarantee that each such stoichiometric compatibility class has an associated equilibrium value for which $A_\kappa(\Psi(c))=0$. However, neither Theorem 4.1 nor Theorem 4.2 makes the requirement that the equilibrium value used in the product-form stationary measure $\pi_\Gamma(\cdot)$ be contained within the stoichiometric compatibility class associated with Γ. Therefore we see that one such c can be used to construct a product-form stationary distribution for every closed, irreducible subset. Conversely, for a given irreducible subset Γ any positive equilibrium value of the system (3.6)-(3.7) can be used to construct $\pi_\Gamma(\cdot)$. This fact seems to be contrary to the uniqueness of the stationary distribution; however, it can be understood through the third conclusion of Theorem 3.2 as follows.

Let Γ be a closed, irreducible subset of the state space with associated positive stoichiometric compatibility class $(y+S)\cap\mathbb{Z}^m_{\geq 0}$, and let $c_1,c_2\in\mathbb{R}^m_{>0}$ be such that $A_\kappa(\Psi(c_1))=A_\kappa(\Psi(c_2))=0$. For $i\in\{1,2\}$ and $x\in\Gamma$, let $\pi_i(x)=M_i c_i^x/x!$, where M_1 and M_2 are normalizing constants. Then for each $x\in\Gamma$

$$\frac{\pi_1(x)}{\pi_2(x)}=\frac{M_1c_1^x}{x!}\frac{x!}{M_2c_2^x}=\frac{M_1}{M_2}\frac{c_1^x}{c_2^x}.$$

For any vector u, we define $(\ln(u))_i=\ln(u_i)$. Then for $x\in\Gamma\subset y+S$

$$\frac{c_1^x}{c_2^x}=e^{x\cdot(\ln c_1-\ln c_2)}=e^{y\cdot(\ln c_1-\ln c_2)}=\frac{c_1^y}{c_2^y}, \tag{4.10}$$

where the second equality follows from the third conclusion of Theorem 3.2. Therefore,

$$\frac{\pi_1(x)}{\pi_2(x)}=\frac{M_1}{M_2}\frac{c_1^y}{c_2^y}. \tag{4.11}$$

Finally,

$$\begin{aligned}1&=\left(M_1\sum_{x\in\Gamma}c_1^x/x!\right)/\left(M_2\sum_{x\in\Gamma}c_2^x/x!\right)\\&=\frac{M_1}{M_2}\left(\frac{c_1^y}{c_2^y}\sum_{x\in\Gamma}c_2^x/x!\right)/\left(\sum_{x\in\Gamma}c_2^x/x!\right)\\&=\frac{\pi_1(x)}{\pi_2(x)},\end{aligned}$$

where the second equality follows from equation (4.10) and the third equality follows from equation (4.11). We therefore see that the stationary measure is independent of the choice of c, as expected.

[2] In the sense of Definition 2.2.

[3] in the sense of Definition 4.4.

5 Examples

Our first example points out that the existence of a product-form stationary distribution for the closed, irreducible subsets of the state space does not necessarily imply independence of the species numbers.

Example 5.1. (Non-independence of species numbers) Consider the simple reversible system

$$S_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} S_2,$$

where k_1 and k_2 are nonzero rate constants. We suppose that $X_1(0) + X_2(0) = N$, and so $X_1(t) + X_2(t) = N$ for all t. This system has two complexes, one linkage class, and the dimension of the stoichiometric compatibility class is one. Therefore it has a deficiency of zero. Since it is also weakly reversible, our results hold. An equilibrium to the system that satisfies the complex balance equation is

$$c = \left(\frac{k_2}{k_1 + k_2}, \frac{k_1}{k_1 + k_2} \right),$$

and the product-form stationary distribution for the system is

$$\pi(x) = M \frac{c_1^{x_1}}{x_1!} \frac{c_2^{x_2}}{x_2!},$$

where $M > 0$ is a normalizing constant. Using that $X_1(t) + X_2(t) = N$ for all t yields

$$\pi_1(x_1) = M \frac{c_1^{x_1}}{x_1!} \frac{c_2^{N-x_1}}{(N-x_1)!} = \frac{M}{x_1!(N-x_1)!} c_1^{x_1} (1-c_1)^{N-x_1},$$

for $0 \leq x_1 \leq N$. After setting $M = N!$, we see that X_1 is binomially distributed. Similarly,

$$\pi_2(x_2) = \binom{N}{x_2} c_2^{x_2} (1-c_2)^{N-x_2},$$

for $0 \leq x_2 \leq N$. Therefore, we trivially have that $P(X_1 = N) = c_1^N$ and $P(X_2 = N) = c_2^N$, but $P(X_1 = N, X_2 = N) = 0 \neq c_1^N c_2^N$, and so X_1 and X_2 are not independent.

Remark. The conclusion of the previous example, that independence does not follow from the existence of a product-form stationary distribution, extends trivially to any network with a conservation relation among the species.

Example 5.2. (First order reaction networks) The results presented below for first order reaction networks are known in both the queueing theory and mathematical chemistry literature. See, for example, [30] and [20]. We present them here to point out how they follow directly from Theorem 4.2.

We begin by defining $|v| = \sum_i v_i$ for any vector $v \in \mathbb{R}^m_{\geq 0}$. We say a reaction network is a *first order reaction network* if $|\nu_k| \in \{0, 1\}$ for each complex $\nu_k \in \mathcal{C}$. Therefore, a network is first order if each entry of the ν_k are zeros or ones, and at most one entry can be a one. It is simple to

show that first order reaction networks necessarily have a deficiency of zero. Therefore, the results of this paper are applicable to all first order reaction networks that are weakly reversible. Consider such a reaction network with only one linkage class (for if there is more than one linkage class we may consider the different linkage classes as distinct networks). We say that the network is *open* if there is at least one reaction, $\nu_k \to \nu_k'$, for which $\nu_k = \vec{0}$. Hence, by weak reversibility, there must also be a reaction for which $\nu_k' = \vec{0}$. If no such reaction exists, we say the network is *closed*. If the network is open we see that $S = \mathbb{R}^m$, $\Gamma = \mathbb{Z}^m_{\geq 0}$ is irreducible, and so by Theorem 4.2 the unique stationary distribution is

$$\pi(x) = \prod_{i=1}^{m} \frac{c_i^{x_i}}{x_i!} e^{-c_i}, \qquad x \in \mathbb{Z}^m_{\geq 0},$$

where $c \in \mathbb{R}^m_{>0}$ is the complexed balanced equilibrium of the associated (linear) deterministic system. Therefore, when in distributional equilibrium, the species numbers are independent and have Poisson distributions. Note that neither the independence nor the Poisson distribution resulted from the fact that the system under consideration was a first order system. Instead both facts followed from Γ being all of $\mathbb{Z}^m_{\geq 0}$.

In the case of a closed, weakly reversible, single linkage class, first order reaction network, it is easy to see that there is a unique conservation relation $X_1(t) + \cdots + X_m(t) = N$, for some N. Thus, in distributional equilibrium $X(t)$ has a multinomial distribution. That is for any $x \in \mathbb{Z}^m_{\geq 0}$ satisfying $x_1 + x_2 + \cdots + x_m = N$

$$\pi(x) = \binom{N}{x_1, x_2, \ldots, x_m} c^x = \frac{N!}{x_1! \cdots x_m!} c_1^{x_1} \cdots c_m^{x_m}, \tag{5.1}$$

where $c \in \mathbb{R}^m_{>0}$ is the equilibrium of the associated deterministic system normalized so that $\sum_i c_i = 1$. As in the case of the open network, we note that the form of the equilibrium distribution does not follow from the fact that the network only has first order reactions. Instead (5.1) follows from the structure of the closed, irreducible communicating classes.

Example 5.3. (Enzyme kinetics I) Consider the possible model of enzyme kinetics given by

$$E + S \rightleftarrows ES \rightleftarrows E + P, \qquad E \rightleftarrows \emptyset \rightleftarrows S, \tag{5.2}$$

where E represents an enzyme, S represents a substrate, ES represents an enzyme-substrate complex, P represents a product, and some choice of rate constants has been made. We note that both E and S are being allowed to enter and leave the system.

The network (5.2) is reversible and has six complexes and two linkage classes. The dimension of the stoichiometric subspace is readily checked to be four, and so the network has a deficiency of zero. Theorem 4.2 applies and so the stochastically modeled system has a product-form stationary distribution of the form (4.2). Ordering the species as $X_1 = E$, $X_2 = S$, $X_3 = ES$, and $X_4 = P$, the reaction vectors for this system include

$$\left\{ \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} -1 \\ -1 \\ 1 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 \\ 0 \\ -1 \\ 1 \end{bmatrix} \right\}.$$

We therefore see that $\Gamma = \mathbb{Z}^4_{\geq 0}$ is the unique closed, irreducible communicating class of the stochastically modeled system and Theorem 4.2 tells us that in distributional equilibrium the species numbers are independent and have Poisson distributions with parameters c_i, which are the complex balanced equilibrium values of the analogous deterministically modeled system.

Example 5.4. (Enzyme kinetics II) Consider the possible model for enzyme kinetics given by

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} E + P, \qquad \emptyset \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} E, \tag{5.3}$$

where the species E, S, ES, and P are as in Example 5.3. We are now allowing only the enzyme E to enter and leave the system. The network is reversible, there are five complexes, two linkage classes, and the dimension of the stoichiometric compatibility class is three. Therefore, Theorem 4.2 implies that the stochastically modeled system has a product-form stationary distribution of the form (4.2). The only conserved quantity of the system is $S + ES + P$, and so $X_2(t) + X_3(t) + X_4(t) = N$ for some $N > 0$ and all t. Therefore, after solving for the normalizing constant, we have that for any $x \in \mathbb{Z}^4_{\geq 0}$ satisfying $x_2 + x_3 + x_4 = N$

$$\pi(x) = e^{-c_1} \frac{c_1^{x_1}}{x_1!} \frac{N!}{x_2! x_3! x_4!} c_2^{x_2} c_3^{x_3} c_4^{x_4} = e^{-c_1} \frac{c_1^{x_1}}{x_1!} \binom{N}{x_2, x_3, x_4} c_2^{x_2} c_3^{x_3} c_4^{x_4},$$

where $c = (k_3/k_{-3}, c_2, c_3, c_4)$ has been chosen so that $c_2 + c_3 + c_4 = 1$. Thus, when the stochastically modeled system is in distributional equilibrium we have that: (a) E has a Poisson distribution with parameter k_3/k_{-3}, (b) $S,\ ES$, and P are multinomially distributed, and (c) E is independent from $S,\ ES$, and P.

5.1 The multiscale nature of reaction networks

Within a cell, some chemical species may be present in much greater abundance than others. In addition, the rate constants κ_k may vary over several orders of magnitude. Consequently, the scaling limit that gives the classical deterministic law of mass action detailed in Section 4.1 may not be appropriate, and a different approach to deriving a scaling limit approximation for the basic Markov chain model must be considered. As a consequence of the multiple scales in a network model, it may be possible to separate the network into subnetworks of species and reactions, each dominated by a time scale of a specific magnitude. Within each subnetwork, the graph structure and stoichiometric properties may determine properties of the asymptotic solutions of the subnetwork.

Example 5.5. Consider the reaction network

$$S + E_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} C \overset{\kappa_3}{\to} P + E_1, \quad E_1 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftarrows}} A + E_2, \quad \emptyset \underset{\kappa_7}{\overset{\kappa_6}{\rightleftarrows}} E_2,$$

where $\emptyset \to E_2$ and $E_2 \to \emptyset$ represent production and degradation of E_2, respectively, S is a substrate being converted to a product P, E_1 and E_2 are enzymes, and A is a substrate that reacts with E_2 allosterically to transform it into an active form.

We suppose that (i) the enzymes E_1, E_2 and the substrate A are in relatively low abundances, (ii) the substrate S has a large abundance of $\mathcal{O}(V)$, and (iii) the reaction rates are also of the order

$\mathcal{O}(V)$. We change notation slightly and denote the number of molecules of species A at time t as $X_A^V(t)$, and similarly for the other species. Further, we denote $X_S^V(t)/V = Z_S^V(t)$. Combined with the conservation relation $X_{E_1}^V + X_C^V + X_A^V = M \in \mathbb{Z}_{>0}$, the scaled equations for the stochastic model are

$$\begin{aligned}
Z_S^V(t) &= Z_S^V(0) - V^{-1}Y_1(V\int_0^t \kappa_1 Z_S^V(s)X_{E_1}^V(s)ds) + V^{-1}Y_2(V\int_0^t \kappa_2 X_C^V(s)ds)\\
X_{E_1}^V(t) &= X_{E_1}^V(0) - Y_1(V\int_0^t \kappa_1 Z_S^V(s)X_{E_1}^V(s)ds) + Y_2(V\int_0^t \kappa_2 X_C^V(s)ds)\\
&\quad + Y_3(V\int_0^t \kappa_3 X_C^V(s)ds) - Y_4(V\int_0^t \kappa_4 X_{E_1}^V(s)ds) + Y_5(V\int_0^t \kappa_5 X_A^V(s)X_{E_2}^V(s)ds)\\
X_A^V(t) &= X_A^V(0) + Y_4(V\int_0^t \kappa_4 X_{E_1}^V(s)ds) - Y_5(V\int_0^t \kappa_5 X_A^V(s)X_{E_2}^V(s)ds)\\
X_{E_2}^V(t) &= X_{E_2}^V(0) + Y_6(V\kappa_6 t) + Y_4(V\int_0^t \kappa_4 X_{E_1}^V(s)ds) - Y_5(V\int_0^t \kappa_5 X_A^V(s)X_{E_2}^V(s)ds)\\
&\quad - Y_7(V\int_0^t \kappa_7 X_{E_2}^V(s)ds),
\end{aligned}$$

where the Y_i are unit-rate Poisson processes. The first equation satisfies

$$Z_S^V(t) = Z_S^V(0) - V^{-1}Y_1(V\int_0^t \kappa_1 Z_S^V(s)\int_{-\infty}^{\infty} x\mu_s^V(dx)ds) + V^{-1}Y_2(V\int_0^t \kappa_2 \int_{-\infty}^{\infty} x\eta_s^V(dx)ds),$$

where $\mu_s^V(A) = I_{\{X_{E_1}^V(s)\in A\}}$ and $\eta_s^V(A) = I_{\{X_C^V(s)\in A\}}$ are the respective occupation measures. Using methods from stochastic averaging (see, for example, [8, 34]), as $V \to \infty$ the fast system is "averaged out:"

$$Z_S(t) = Z_S(0) - \int_0^t \kappa_1 Z_S(s)\int_{-\infty}^{\infty} x\mu_s(dx)ds + \int_0^t \kappa_2 \int_{-\infty}^{\infty} x\eta_s(dx)ds, \tag{5.4}$$

where μ_s and η_s are the stationary distributions of X_{E_1} and X_C, respectively, of the fast subsystem with $Z_S(s)$ held constant (assuming a stationary distribution exists). This reduced network (i.e. the fast subsystem) is

$$A + E_2 \underset{\kappa_4}{\overset{\kappa_5}{\rightleftarrows}} E_1 \underset{\kappa_2+\kappa_3}{\overset{\kappa_1 Z_S(s)}{\rightleftarrows}} C, \qquad \emptyset \underset{\kappa_7}{\overset{\kappa_6}{\rightleftarrows}} E_2. \tag{5.5}$$

Setting $z = Z_S(s)$ we have the following equilibrium relations for the moments of the above network

$$\begin{aligned}
\kappa_4\mathbb{E}[X_{E_1}] - \kappa_5\mathbb{E}[X_A X_{E_2}] &= 0\\
-(\kappa_1 z + \kappa_4)\mathbb{E}[X_{E_1}] + (\kappa_2+\kappa_3)\mathbb{E}[X_C] + \kappa_5\mathbb{E}[X_A X_{E_2}] &= 0\\
\kappa_6 + \kappa_4\mathbb{E}[X_{E_1}] - \kappa_5\mathbb{E}[X_A X_{E_2}] - \kappa_7\mathbb{E}[X_{E_2}] &= 0\\
\mathbb{E}[X_{E_1}] + \mathbb{E}[X_C] + \mathbb{E}[X_A] &= M.
\end{aligned} \tag{5.6}$$

$\mathbb{E}[X_{E_1}]$ and $\mathbb{E}[X_C]$, which are both functions of z and needed in equation (5.4), can not be explicitly solved for via the above equations without extra tools as (5.6) is a system of four equations

with five unknowns. This situation arises frequently as it stems from the nonlinearity of the system. However, the network (5.5) consists of five complexes, two connected components, and the dimension of its stoichiometric subspace is three. Therefore, its deficiency is zero. As it is clearly weakly reversible, Theorem 4.1 applies and, due to the product form of the distribution and the unboundedness of the support of X_{E_2}, it is easy to argue that X_{E_2} is independent of X_A, X_{E_1}, and X_C when in equilibrium. Thus, $\mathbb{E}[X_A X_{E_2}] = \mathbb{E}[X_A]\mathbb{E}[X_{E_2}]$ and the first moments can be solved for as functions of $Z_S(s)$. After solving and inserting these moments, (5.4) becomes

$$Z_S(t) = Z_S(0) - \int_0^t \frac{\kappa_1\kappa_3\kappa_5\kappa_6 M Z_S(s)}{(\kappa_5\kappa_6 + \kappa_7\kappa_4)(\kappa_2 + \kappa_3) + \kappa_1\kappa_5\kappa_6 Z_S(s)} ds,$$

which is Michaelis-Menten kinetics.

6 More general kinetics

In this section we extend our results to systems with more general kinetics than stochastic mass action. The generalizations we make are more or less standard for the types of results presented in this paper (see, for example, [30], Section 8.5, [38], Chapter 9). What is surprising, however, is that the conditions of the deficiency zero theorem of Feinberg (which are conditions on mass-action deterministic systems) are also sufficient to guarantee the existence of stationary distributions of stochastically modeled systems even when the intensity functions are not given by (3.4). It is interesting to note that the generalizations made here for the stochastic deficiency zero Theorem 4.2 are similar to those made in [37], which generalized Feinberg's deficiency zero Theorem 3.1 in the deterministic setting.

Suppose that the intensity functions of a stochastically modeled system are given by

$$\lambda_k(x) = \kappa_k \prod_{i=1}^{m} \prod_{j=0}^{\nu_{ik}-1} \theta_i(x_i - j) = \kappa_k \prod_{i=1}^{m} \theta_i(x_i)\theta_i(x_i - 1)\theta_i(x_i - (\nu_{ik} - 1)), \tag{6.1}$$

where the κ_k are positive constants, $\theta_i : \mathbb{Z} \to \mathbb{R}_{\geq 0}$, $\theta_i(x) = 0$ if $x \leq 0$, and we use the convention that $\prod_{j=0}^{-1} a_j = 1$ for any $\{a_j\}$. Note that the final condition allows us to drop the indicator functions of (3.4). As pointed out in [30], the function θ_i should be thought of as the "rate of association" of the ith species. We give a few interesting choices for θ_i. If $\theta_i(x_i) = x_i$ for $x_i \geq 0$, then (6.1) is stochastic mass-action kinetics. However, if for $x_i \geq 0$

$$\theta_i(x_i) = \frac{v_i x_i}{k_i + x_i}, \tag{6.2}$$

for some positive constants k_i and v_i, then the system has a type of stochastic Michaelis-Menten kinetics ([29], Chapter 1). Finally, if $|\nu_k| \in \{0, 1\}$ and $\theta_i(x_i) = \min\{n_i, x_i\}$ for $x_i \geq 0$, then the dynamical system models an $M/M/n$ queueing network in which the ith species (and in this case complex) represents the queue length of the ith queue, which has n_i servers who work on a first come, first serve basis.

The main restriction imposed by (6.1) is that for any reaction for which the ith species appears in the source complex, the rate of that reaction must depend upon X_i via $\theta_i(X_i)$ only. Therefore,

if, say, the ith species is governed by the kinetics (6.2), then the constants k_i and v_i must be the same for each intensity which depends upon X_i (although the v_i may be incorporated into the rate constants κ_k, and so the real restriction is on the constant k_i). However, systems with intensities given by (6.1) are quite general in that different kinetics can be incorporated into the same model through the functions θ_i. For example, if in a certain system species S_1 is modeled to be governed by Michaelis-Menten kinetics (6.2) and species S_2 is modeled to be governed by mass-action kinetics, then the reaction $S_1 + S_2 \to \nu'_k$ would have intensity

$$\lambda_k(x) = \kappa_k \frac{v_1 x_1}{k_1 + x_1} x_2,$$

for some constant κ_k.

In following we use the convention that $\prod_{j=1}^{0} a_j = 1$ for any choice of $\{a_j\}$.

Theorem 6.1. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a stochastically modeled chemical reaction network with intensity functions* (6.1)*. Suppose that the associated mass-action deterministic system with rate constants $\{\kappa_k\}$ has a complex balanced equilibrium $c \in \mathbb{R}^m_{>0}$. Then the stochastically modeled system admits the stationary distribution*

$$\pi(x) = M \prod_{i=1}^{m} \frac{c_i^{x_i}}{\prod_{j=1}^{x_i} \theta_i(j)}, \qquad x \in \mathbb{Z}^m_{\geq 0}, \tag{6.3}$$

where $M > 0$ is a normalizing constant, provided that (6.3) *is summable. If $\mathbb{Z}^m_{\geq 0}$ is irreducible, then* (6.3) *is the unique stationary distribution, whereas if $\mathbb{Z}^m_{\geq 0}$ is not irreducible then the π_Γ of equation* (4.1) *are given by the product-form stationary distributions*

$$\pi_\Gamma(x) = M_\Gamma \prod_{i=1}^{m} \frac{c_i^{x_i}}{\prod_{j=1}^{x_i} \theta_i(j)}, \qquad x \in \Gamma, \tag{6.4}$$

and $\pi_\Gamma(x) = 0$ otherwise, where $M_\Gamma > 0$ is a normalizing constant, provided that (6.4) *is summable.*

Proof. The proof consists of plugging (6.3) and (6.1) into equation (3.5) and verifying that c being a complex balanced equilibrium is sufficient. The details are similar to before and so are omitted. □

Remark. We simply remark that just as Theorem 4.2 followed directly from Theorem 4.1, the results of Theorem 6.1 hold, independent of the choice of rate constants κ_k, so long as the associated network is weakly reversible and has a deficiency of zero.

Example 6.2. Consider a network, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, that is weakly reversible and has a deficiency of zero. Suppose we have modeled the dynamics stochastically with intensity functions given by (6.1) with each θ_i given via (6.2) for some choice of $v_i > 0$ and k_i a nonnegative integer. That is, we consider a system endowed with stochastic Michaelis-Menten kinetics. Then,

$$\prod_{j=1}^{x_i} \theta_i(j) = \prod_{j=1}^{x_i} \frac{v_i j}{k_i + j} = v_i^{x_i} / \binom{k_i + x_i}{x_i}.$$

Thus, our candidate for a stationary distribution is

$$\pi(x) = M \prod_{i=1}^{m} \frac{c_i^{x_i}}{\prod_{j=1}^{x_i} \theta_i(j)} = M \prod_{i=1}^{m} \binom{k_i + x_i}{x_i} \left(\frac{c_i}{v_i}\right)^{x_i}. \tag{6.5}$$

Noting that

$$\binom{k_i + x_i}{x_i} = O(x_i^{k_i}), \quad x_i \to \infty,$$

we see that $\pi(x)$ given by (6.5) is summable if $c_i < v_i$ for each species S_i whose possible abundances are unbounded. In this case, (6.5) is indeed a stationary distribution for the system. We note that the condition $c_i < v_i$ for each species S_i is both necessary and sufficient to guarantee summability if $Z_{\geq 0}^m$ is irreducible, as in such a situation the species numbers are independent.

Example 6.3. In [35], Levine and Hwa computed and analyzed the stationary distributions of different stochastically modeled chemical reaction systems with Michaelis-Menten kinetics (6.2). The models they considered included among others: directed pathways ($\emptyset \to S_1 \to S_2 \to \cdots \to S_L \to \emptyset$), reversible pathways ($\emptyset \to S_1 \leftrightarrows S_2 \leftrightarrows \cdots \leftrightarrows S_L \to \emptyset$), pathways with dilution of intermediates ($S_i \to \emptyset$), and cyclic pathways ($S_L \to S_1$). Each of the models considered in [35] is biologically motivated and has a first order reaction network ($|\nu_k| \in \{0, 1\}$, see Example 5.2), which guarantees that they have a deficiency of zero. Further, the networks of the models considered are weakly reversible; therefore, the results of the current paper, and in particular Theorem 6.1 and the remark that follows, apply so long as the restrictions discussed in the paragraph preceding Theorem 6.1 are met. While these restriction are not always met (for example, dilution is typically modeled with a linear intensity function and there is no reason for the k_i of a forward and a backward reaction for a species S_i in a reversible pathway to be the same), they found that the stationary distributions for these models are either of product form (when the restrictions are met) or near product form (when the restrictions are not met). Further, because $\mathbb{Z}_{\geq 0}^m$ is irreducible in each of these models, the product form of the distribution implies that the species numbers are independent. It is then postulated that the independence of the species numbers could play an important, beneficial, biological role (see [35] for details). Similar to the conclusions we drew in Example 5.2, Theorem 6.1 and the remark that follows point out how the models analyzed in [35] are actually special cases of a quite general family of systems that have both the product form and independence properties, and that these properties may be more widespread, and taken advantage of by living organisms, than previously thought.

We return to the result of Example 6.2 pertaining to the summability of (6.5) and show that this can be generalized in the following manner.

Theorem 6.4. *Suppose that for some closed, irreducible $\Gamma \subset \mathbb{Z}_{\geq 0}^m$, $\pi_\Gamma : \Gamma \to \mathbb{R}_{\geq 0}$ satisfies*

$$\pi_\Gamma(x) = M \prod_{i=1}^{m} \frac{c_i^{x_i}}{\prod_{j=1}^{x_i} \theta_i(j)},$$

for some $c \in \mathbb{R}_{>0}^m$ and $M > 0$, where $\theta_i : \mathbb{Z}_{\geq 0} \to \mathbb{R}_{\geq 0}$ for each i. Then $\pi_\Gamma(x)$ is summable if for each i for which $\sup\{x_i \mid x \in \Gamma\} = \infty$ we have that $\theta_i(j) > c_i + \epsilon$ for some $\epsilon > 0$ and j sufficiently large.

Proof. The conditions of the theorem immediately imply that there are positive constants C and ρ for which $\pi_\Gamma(x) < Ce^{-\rho|x|}$, for all $x \in \Gamma$, which implies that $\pi_\Gamma(x)$ is summable. □

It is tempting to believe that the conditions of Theorem 6.4 are in fact necessary, as in the case when $Z^m_{\geq 0}$ is irreducible. The following simple example shows this not to be the case.

Example 6.5. Consider the reaction system with network

$$\emptyset \rightleftarrows S_1 + S_2,$$

where the rate of the reaction $\emptyset \to S_1 + S_2$ is $\lambda_1(x) = 1$, and the rate of the reaction $S_1 + S_2 \to \emptyset$ is $\lambda_2(x) = 1 \times \theta_1(x_1)\theta_2(x_2)$, where

$$\theta_1(x_1) = \frac{3x_1}{1+x_1}, \quad \theta_2(x_2) = \frac{(1/2)x_2}{1+x_2}.$$

Assume further that $X_1(0) = X_2(0)$. For the more physically minded readers, we note that this model could describe a reaction system for which there is a chemical complex $C = S_1S_2$ that sporadically breaks into its chemical constituents, which may then re-form. The complex C may be present in such high numbers relative to free S_1 and S_2 that we choose to model it as fixed, which leads to the above reaction network.

We note that in this case, the reaction rates $\{\kappa_k\}$ for the corresponding mass-action deterministic system are both equal to one, and so an equilibrium value guaranteed to exist for the deterministically modeled system by the deficiency zero theorem is $c = (1, 1)$. This system does not satisfy the assumptions of Theorem 6.4 because both X_1 and X_2 are unbounded and $\lim_{j\to\infty} \theta_2(j) = 1/2 < 1 = c_2$. However, for any $x \in \Gamma = \{x \in \mathbb{Z}^2_{\geq 0} \,:\, x_1 = x_2\}$,

$$\pi_\Gamma(x) = \binom{1+x_1}{x_1}\left(\frac{1}{3}\right)^{x_1}\binom{1+x_2}{x_2}\left(\frac{1}{(1/2)}\right)^{x_2} = \binom{1+x_1}{x_1}^2\left(\frac{2}{3}\right)^{x_1},$$

which is summable over Γ.

For the most general kinetics handled in this paper, we let the intensity functions of a stochastically modeled system be given by

$$\lambda_k(x) = \kappa_k \frac{\theta(x)}{\theta(x-\nu_k)} \prod_{\ell=1}^{m} 1_{\{x_\ell \geq \nu_{\ell k}\}}, \tag{6.6}$$

where the κ_k are positive constants, and $\theta : \mathbb{Z}^m \to \mathbb{R}_{>0}$. Note that if

$$\theta(x) = \prod_{i=1}^{m}\prod_{j=1}^{x_i} \theta_i(j),$$

for some functions θ_i, then (6.6) is equivalent to (6.1), and so the following theorem implies Theorem 6.1. It's proof is similar to the previous theorems and so is omitted.

Theorem 6.6. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a stochastically modeled chemical reaction network with intensity functions* (6.6)*. Suppose that the associated mass-action deterministic system with rate constants $\{\kappa_k\}$ has a complex balanced equilibrium $c \in \mathbb{R}^m_{>0}$. Then the stochastically modeled system admits the stationary distribution*

$$\pi(x) = M \frac{1}{\theta(x)} \prod_{i=1}^{m} c_i^{x_i}, \quad x \in \mathbb{Z}^m_{\geq 0}, \tag{6.7}$$

where $M > 0$ is a normalizing constant, provided that (6.7) *is summable. If $\mathbb{Z}^m_{\geq 0}$ is irreducible, then* (6.7) *is the unique stationary distribution, whereas if $\mathbb{Z}^m_{\geq 0}$ is not irreducible then the π_Γ of equation* (4.1) *are given by the product-form stationary distributions*

$$\pi_\Gamma(x) = M_\Gamma \frac{1}{\theta(x)} \prod_{i=1}^{m} c_i^{x_i}, \qquad x \in \Gamma, \tag{6.8}$$

and $\pi_\Gamma(x) = 0$ otherwise, where $M_\Gamma > 0$ is a normalizing constant, provided that (6.8) *is summable.*

Remark. Similar to the remark following Theorem 6.1, we point out that the results of Theorem 6.6 hold, independent of the choice of rate constants κ_k, so long as the associated network is weakly reversible and has a deficiency of zero.

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References

[1] David F. Anderson, *A modified next reaction method for simulating chemical systems with time dependent propensities and delays*, J. Chem. Phys. **127** (2007), no. 21, 214107.

[2] ———, *Global asymptotic stability for a class of nonlinear chemical equations*, SIAM J. Appl. Math **68** (2008), 1464 – 1476.

[3] ———, *Incorporating postleap checks in tau-leaping*, J. Chem. Phys. **128** (2008), no. 5, 054103.

[4] David F. Anderson and Gheorghe Craciun, *Reduced reaction networks and persistence of chemical systems*, in preparation.

[5] David F. Anderson, Arnab Ganguly, and Thomas G. Kurtz, *Error analysis of tau-leap simulation methods*, submitted, arxiv:0909.4790v1, 2009.

[6] David F. Anderson and Anne Shiu, *The dynamics of weakly reversible population processes near facets*, To appear in SIAM J. Appl. Math., 2010.

[7] David Angeli, Patrick De Leenheer, and Eduardo D. Sontag, *A petri net approach to the study of persistence in chemical reaction networks*, Mathematical Biosciences **210** (2007), 598–618.

[8] Karen Ball, Thomas G. Kurtz, Lea Popovic, and Greg Rempala, *Asymptotic analysis of multiscale approximations to reaction networks*, Ann. Appl. Prob. **16** (2006), no. 4, 1925–1961.

[9] Yang Cao, Daniel T. Gillespie, and Linda R. Petzold, *Efficient step size selection for the tau-leaping simulation method*, J. Chem. Phys. **124** (2006), 044109.

[10] Hong Chen and David D. Yao, *Fundamentals of queueing networks*, Applications of Mathematics (New York), vol. 46, Springer-Verlag, New York, 2001, Performance, asymptotics, and optimization, Stochastic Modelling and Applied Probability. MR MR1835969 (2003c:60149)

[11] Gheorghe Craciun and Martin Feinberg, *Multiple equilibria in complex chemical reaction networks: I. the injectivity property*, Siam J. Appl. Math **65** (2005), no. 5, 1526–1546.

[12] ———, *Multiple equilibria in complex chemical reaction networks: Ii. the species-reactions graph*, Siam J. Appl. Math **66** (2006), no. 4, 1321–1338.

[13] Gheorghe Craciun, Yangzhong Tang, and Martin Feinberg, *Understanding bistability in complex enzyme-driven networks*, PNAS **103** (2006), no. 23, 8697–8702.

[14] Stewart N. Ethier and Thomas G. Kurtz, *Markov processes: Characterization and convergence*, John Wiley & Sons, New York, 1986.

[15] Martin Feinberg, *Complex balancing in general kinetic systems*, Arch. Rational Mech. Anal. **49** (1972), 187–194.

[16] ———, *Lectures on chemical reaction networks*, Delivered at the Mathematics Research Center, Univ. Wisc.-Madison. Available for download at http://www.che.eng.ohio-state.edu/∼feinberg/LecturesOnReactionNetworks, 1979.

[17] ———, *Chemical reaction network structure and the stability of complex isothermal reactors - I. the deficiency zero and deficiency one theorems, review article 25*, Chem. Eng. Sci. **42** (1987), 2229–2268.

[18] ———, *Necessary and sufficient conditions for detailed balancing in mass action systems of arbitrary complexity*, Chem. Eng. Sci. **44** (1989), no. 9, 1819–1827.

[19] ———, *Existence and uniqueness of steady states for a class of chemical reaction networks*, Arch. Rational Mech. Anal. **132** (1995), 311–370.

[20] Chetan Gadgil, Chang Hyeong Lee, and Hans G. Othmer, *A stochastic analysis of first-order reaction networks*, Bull. Math. Bio. **67** (2005), 901–946.

[21] Michael A. Gibson and Jehoshua Bruck, *Efficient exact stochastic simulation of chemical systems with many species and many channels*, J. Phys. Chem. A **105** (2000), 1876–1889.

[22] Dan T. Gillespie, *A general method for numerically simulating the stochastic time evolution of coupled chemical reactions*, J. Comput. Phys. **22** (1976), 403–434.

[23] ———, *Exact stochastic simulation of coupled chemical reactions*, J. Phys. Chem. **81** (1977), no. 25, 2340–2361.

[24] ———, *Approximate accelerated simulation of chemically reaction systems*, J. Chem. Phys. **115** (2001), no. 4, 1716–1733.

[25] Jeremy Gunawardena, *Chemical reaction network theory for in-silico biologists*, Notes available for download at http://vcp.med.harvard.edu/papers/crnt.pdf, 2003.

[26] Fritz J. M. Horn, *Necessary and sufficient conditions for complex balancing in chemical kinetics*, Arch. Rat. Mech. Anal. **49** (1972), no. 3, 172–186.

[27] ———, *Stability and complex balancing in mass-action systems with three complexes*, Proc. Royal Soc. A **334** (1973), 331–342.

[28] Fritz J. M. Horn and Roy Jackson, *General mass action kinetics*, Arch. Rat. Mech. Anal. **47** (1972), 81–116.

[29] James Keener and James Sneyd, *Mathematical physiology*, Springer-Verlag, New York, 1998.

[30] Frank P. Kelly, *Reversibility and stochastic networks*, John Wiley & Sons Ltd., Chichester, 1979, Wiley Series in Probability and Mathematical Statistics. MR MR554920 (81j:60105)

[31] Thomas G. Kurtz, *The relationship between stochastic and deterministic models for chemical reactions*, J. Chem. Phys. **57** (1972), no. 7, 2976–2978.

[32] ———, *Strong approximation theorems for density dependent Markov chains*, Stoch. Proc. Appl. **6** (1977/78), 223–240.

[33] ———, *Approximation of population processes*, CBMS-NSF Reg. Conf. Series in Appl. Math.: 36, SIAM, 1981.

[34] ———, *Averaging for martingale problems and stochastic approximation*, Applied Stochastic Analysis, Lecture Notes in Control and Information Sciences, vol. 77, Springer, Berlin, 1992, pp. 186–209.

[35] Erel Levine and Terence Hwa, *Stochastic fluctuations in metabolic pathways*, PNAS **104** (2007), no. 22, 9224–9229.

[36] Richard Serfozo, *Introduction to stochastic networks*, Applications of Mathematics (New York), vol. 44, Springer-Verlag, New York, 1999. MR MR1704237 (2000k:60193)

[37] Eduardo D. Sontag, *Structure and stability of certain chemical networks and applications to the kinetic proofreading of t-cell receptor signal transduction*, IEEE Trans. Auto. Cont. **46** (2001), no. 7, 1028–1047.

[38] Peter Whittle, *Systems in stochastic equilibrium*, John Wiley & Sons, Inc., New York, NY, USA, 1986.